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10/500,047	02/08/2005	Jon H. Rasmussen	C2432.0057	9121

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EXAMINER
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KOSAR, ANDREW D

ART UNIT	PAPER NUMBER
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1654

MAIL DATE	DELIVERY MODE
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09/20/2007

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

# Office Action Summary

Application No.

10/500,047

Applicant(s)

RASMUSSEN ET AL.

Examiner

Andrew D. Kosar

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 28 June 2007.
- 2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 14-24 and 26-30 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 14-24 26-30 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\*-See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

## DETAILED ACTION

### *Response to Amendments/Arguments*

Applicant's amendments and arguments filed June 28, 2007 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed is herein withdrawn.

It is noted that Applicant argues that additional references, e.g. Hubbs and Veber (page 11, Remarks) "add nothing to the rejection of this claim [claim 26]" and that Gefter "has been cited to show that AA2 can be a natural amino acid but any reference to AA2 first appears in instant claim 15, not 14". Respectfully, the rejections are cumulative, and thus it would be improper to exclude claims which are rejected by fewer references (e.g. A in view of B) when bringing in a further reference to reject further limitations (e.g., A in view of B in further view of C), particularly when the previous rejection and teachings are incorporated therein.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15-19 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 recites, "such as Boc" which renders the claims vague and indefinite, as it is unclear whether the Boc is a limitation in the claim or merely exemplary of protecting groups that can be employed in the method. It is noted that Applicant corrected this indefiniteness for claim 20 in the response.

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Furthermore, a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

**Claims 26** remains rejected under 35 U.S.C. 103(a) as being unpatentable over FUNK in view of O'NEILL for the reasons of record and those set forth below.

The instant claim is drawn to the peptide Boc-D-2Nal-D-4CIPhe-D-3Pal-OH.

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Applicant argues that the product is not anticipated, arguing that the examiner has relied upon the instant application to arrive at the instant peptide. Respectfully, the examiner disagrees. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Here, Ac and Boc are both well known and widely used protecting groups, and thus one would clearly understand them to be equivalents, particularly in synthetic applications. Additionally, Funk taught the esterified form of the instantly claimed peptide, as shown previously, and again is an obvious variant of the instantly claimed compound. One would reasonably conclude that the compounds would find similar utility, particularly in synthesis as shown previously, as they are structurally related, differing by either an ester group (C-terminal protecting group) or the Ac/Boc (N-terminal protecting group).

Funk teaches the peptide Ac-D-2Nal-D-4ClPhe-D-3Pal-OH (e.g. Example 45, column 40, line 39).

Funk additionally teaches the peptides Boc-D-2Nal-D-4ClPhe-D-3Pal-OMe, Boc-D-2Nal-D-4ClPhe-D-3Pal-OAll and Boc-D-2Nal-D-4ClPhe-D-3Pal-OBzl (e.g. claim 20; column 13, lines 5-7; synthesis in Example 25, column 24).

Further, Funk teaches the synthesis D-2Nal-D-4ClPhe-D-3Pal-OH

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O'Neill teaches that nitrogen protecting groups are known in the art and, "include[e] t-BOC, CBZ, methyl, benzyl, trifluoroacetyl, acetyl and benzoyl. (column 13, line 65 to column 14, line 61).

The difference between that which is claimed and the teachings of Funk, is that while Funk teaches the peptide with an N-acetyl group, or the Boc protected peptide which has been esterified, Funk does not teach the Boc protected peptide which has not been esterified.

The MPEP states, "A *prima facie* case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities. "An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." *In re Payne*, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). See *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) and *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991)." See MPEP § 2144.09.

Here, the compounds of Funk differ from the instant claims either at the N-terminus (acetyl vs Boc protecting group) or at the C-terminus (H vs methyl). The compounds are both used in further synthesis of LHRH analogs, and acetyl and Boc are both well known N-protecting groups. Thus, it would have been obvious at the time of the invention to have made Boc protected peptide, Boc-D-2Nal-D-4ClPhe-D-3Pal-OH, with the expectation that the compound would function as the N-acetyl counterpart in the synthesis of LHRH analogs. One would have been motivated to have made the Boc protected peptide in order to make a compound that would function similarly in the synthesis of LHRH analogs. One would have had a reasonable expectation for success in making the Boc-protected peptide, since the N-acetyl

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peptide is known, and the esterified Boc-protected peptide is known and incorporation of a protecting group is widely practiced in the peptide arts.

Furthermore, Funk and O'Neill are relied upon for the reasons discussed above. If not expressly taught by the references, based upon the overall beneficial teaching provided with respect to the LHRH analog precursors and N-protecting groups, the adjustments of particular conventional working conditions (e.g., selecting one or more suitable protecting groups), is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

**Claims 14-16, 18, 20-22 and 26-30** are/remain rejected under 35 U.S.C. 103(a) as being unpatentable over Funk, *supra*, in view of O'Neill, as applied to claim 26 *supra*, and in further view of HUBBS (US Patent 5,322,931) and VEBER (US Patent 4,098,777), for the reasons of record and those set forth below.

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The instant claims are further drawn to the method of making X-D-2Nal-D-4ClPhe-D-3Pal-OH where X is Ac or Boc, and to the method of making LHRH antagonists using said compounds. The teachings of Funk and O'Neill are presented *supra*.

Applicant argues that the examiner, "makes no attempt to point out where Funk teaches the sequence of the three mandatory steps in claim 14, other than making some vague reference to "basic methods claimed"" (page 12, remarks) and asserts that there is no teaching or suggestion in Funk, alone or in combination, to teach or suggest the specific consecutive steps. Applicant argues further than the increased yield is unexpected when compared to Funk.

Respectfully, the examiner disagrees. The statement relied upon by Applicant is misrepresented, and is merely the statement the examiner utilized as the basis for formulating the rejection. The teachings of Funk, in reference to the method, were clearly delineated and the three mandatory steps are clearly identified stating, "Funk teaches the synthesis of synthesis of the protected compound P<sup>1</sup>-D-2Nal-D-4ClPhe-D-3Pal-O-P<sup>4</sup> (Scheme III, column 11) from reaction of P<sup>1</sup>-D-2Nal-OH with P<sup>1</sup>-D-4ClPhe-D-3Pal-O-P<sup>4</sup>. P<sup>1</sup>-D-4ClPhe-D-3Pal-O-P<sup>4</sup> is synthesized from P<sup>1</sup>-D-4ClPhe-OH and the HCl salt of D-3Pal-O-P<sup>4</sup>." Specific reference to the specification of Funk was provided where the method steps were found. Furthermore, it appears Applicant would have the examiner provide anticipatory art in order to reject the claims under obviousness. Furthermore, HONSu is well known to be used in coupling, and thus one would readily use any coupling agent to form the amide bond, and one would use any protecting group, as many are well known and widely used in peptide synthesis.

With regards to the comparison provided by Applicant, respectfully, the examiner is unable to agree that the result is "unexpected" result, as the final products relied upon in the

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comparison are structurally different and are not a side-by-side comparison necessary to show that the instant method provides an unexpected result of increased yield.

Additionally, it should be noted that KSR forecloses the argument that a **specific** teaching, suggestion, or motivation is required to support a finding of obviousness (*See Ex Parte Smith*, USPQ2d, slip op. 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing *KSR v. Teleflex*, 82 USPQ2d 1396).

Funk teaches the formation of Ac-D-2Nal-D-4ClPhe-D-3Pal-Ser(Bzl)-NMeTyr(Cl<sub>2</sub>Bzl)-D-Lys(Nic)-Leu-Lys(iPr)-Pro-D-Ala-NH<sub>2</sub> from the reaction of Ac-D-2Nal-D-4ClPhe-D-3Pal-OH with Boc-Ser(Bzl)-NMeTyr(Cl<sub>2</sub>Bzl)-D-Lys(Nic)-Leu-Lys(iPr)-Pro-D-Ala-NH<sub>2</sub>. (Example 40, column 40).

Funk further teaches the synthesis of synthesis of the protected compound P<sup>1</sup>-D-2Nal-D-4ClPhe-D-3Pal-O-P<sup>4</sup> (Scheme III, column 11) from reaction of P<sup>1</sup>-D-2Nal-OH with P<sup>1</sup>-D-4ClPhe-D-3Pal-O-P<sup>4</sup>. P<sup>1</sup>-D-4ClPhe-D-3Pal-O-P<sup>4</sup> is synthesized from P<sup>1</sup>-D-4ClPhe-OH and the HCl salt of D-3Pal-O-P<sup>4</sup>.

Funk teaches the formation of Ac-D-2Nal-D-4ClPhe-D-3Pal-Ser(Bzl)-NMeTyr(Cl<sub>2</sub>Bzl)-D-Lys(Nic)-Leu-Lys(iPr)-Pro-D-Ala-NH<sub>2</sub> from the reaction of Ac-D-2Nal-D-4ClPhe-D-3Pal-OH with Boc-Ser(Bzl)-NMeTyr(Cl<sub>2</sub>Bzl)-D-Lys(Nic)-Leu-Lys(iPr)-Pro-D-Ala-NH<sub>2</sub>. (Example 40, column 40).

Hubbs teaches, "The condensation reaction of the two fragments can be accomplished by standard techniques, such as treatment of the two peptide fragments with condensation reagents such as a dehydrating agent (e.g. dicyclohexylcarbodiimide (DCC)) and an activating agent (e.g.

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N-hydroxysuccinimide (HONSu)) in an organic solvent. In one preferred embodiment, the activating agent is also a racemization inhibitor (e.g. HONSu)." (column 10, lines 5-13).

Veber teaches that OH protecting groups for serine are benzoyl, t-butyl and benzyl (column 6, lines 36-39) and protecting groups for other amino acids, e.g. Lys (column 9)

The difference between that which is claimed and the teachings of Funk, is that while Funk teaches the basic methods claimed, Funk does not specifically teach the use of HONSu in the coupling step or the specific use of tBu protection of side chains.

It would have been obvious to one of skill in the art to have used HONSu in the synthesis methods in order to inhibit racemization of the product. One would have been motivated to have used HONSu because in addition to being an activating agent in the coupling step, HONSu is a racemization inhibitor. One would have had a reasonable expectation for success in using HONSu in the method of making the LHRH precursors and antagonists, as the method is generally taught by Funk and the use of HONSu in peptide synthesis is known in the art as an activator for coupling that is also an inhibitor of racemization.

With regards to the different protecting groups, if not expressly taught by the references above, based upon the overall beneficial teaching provided with respect to the LHRH analog precursors and N-protecting groups and/or side chain protecting groups, the adjustments of particular conventional working conditions (e.g., selecting one or more suitable protecting groups), is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12

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USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

**Claims 14-24 and 26-30** are/remain rejected under 35 U.S.C. 103(a) as being unpatentable over Funk, *supra*, in view of O'Neill, Hubbs and Veber, as applied to claims 14-16, 18, 20-22, 25 and 26 *supra*, and in further view of GEFTER (US Patent 6,699,833 B1).

The claims are additionally drawn to synthesis of the LHRH analog where AA2 is D-Asn. The teachings of Funk, O'Neill, Hubbs and Veber are presented *supra*.

Applicant argues Gefter does not rectify the deficiencies and is improperly applied to claim 14 (and dependent claims therein). Respectfully, the examiner disagrees. As stated above, the obviousness of claims 14-16, 18, 20-22 and 26, has not been overcome, and thus Gefter is properly relied upon to rectify a deficiency/support a missing element from the previous rejection.

Gefter teaches the LHRH analog where AA2 is D-Asn (e.g. claim 26).

The difference between that which is instantly claimed, and the teachings of Gefter, is that while Gefter teaches the product formed, Gefter does not teach the synthesis as instantly claimed.

It would have been obvious to have synthesized the product using any synthetic methodology, including synthesis by the method of Funk as presented *supra*. One would have been motivated to have synthesized the peptide via any means, including modifying the method of Funk to use protecting groups and HONSu, in order to synthesize the compound and to inhibit racemization of the product. One would have had a reasonable expectation for success in practicing the method to make the product with AA2 being D-Asn, as peptide synthesis is well known and widely used in the art.

With regards to the different protecting groups, if not expressly taught by the references above, based upon the overall beneficial teaching provided with respect to the LHRH analog precursors and N-protecting groups and/or side chain protecting groups, the adjustments of particular conventional working conditions (e.g., selecting one or more suitable protecting groups), is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

*Conclusion*

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Andrew D. Kosar whose telephone number is (571)272-0913. The examiner can normally be reached on Monday - Friday 08:00 - 16:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571)272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Andrew D. Kosar  
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